Remarks

Claims 1-40 are pending. Claims 1-12 are under examination and have been rejected. Claims 13-40 have been withdrawn from consideration pursuant to a restriction requirement.

Response to the Rejections

(1) Rejection of Claims 2 and 7 under 35 U.S.C. § 112 Second Paragraph.

The examiner has rejected claims 2 and 7 under 35 U.S.C. § 112 for being allegedly indefinite in the recitation of the term "substantially free" as applied to the optical purity of the (*R*) and (*S*) enantiomers. The applicants respectfully traverse.

The examiner is respectfully reminded that the definiteness requirement of 35 U.S.C. § 112 is satisfied by "claims which define the patentable subject matter with a reasonable degree of particularity and distinctness." MPEP 2173.02 (emphasis in the original). Further,

> [d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

Id.

The examiner does not explain why the term "substantially free" is considered to be vague and indefinite. Applicants respectfully point out that the term "substantially free" is, in fact, explicitly defined in the specification (see p. 17 lines 9-13), which states that an enantiomer "substantially free" of the other enantiomer means that the composition comprises 80% or more by weight of the one enantiomer (and thus, by implication, 20% or less of the other enantiomer). The meaning of the term is perfectly clear when interpreted

"not in a vacuum, but in light of ... [t]he content of the particular application disclosure". Reconsideration of the rejection is therefore respectfully requested.

(2) Rejection of Claims 1 and 12 under 35 U.S.C. § 102(b).

The examiner has rejected claims 1 and 12 under 35 U.S.C. § 102(b) as being allegedly anticipated by Tomori *et al. (J. Chromatog.* **1982**, *241*, 88-99) ("Tomori"). The applicants respectfully traverse.

The examiner states that Tomori discloses a solution of 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine in chloroform, while U.S. Patent No. 4,025,528 (the '528 patent) allegedly discloses that chloroform is a pharmaceutically acceptable carrier.

Applicants respectfully disagree with the examiner that Tomori discloses a pharmaceutical composition within the scope of claims 1 and 12.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131 citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Tomori fails to describe each and every element required by claims 1 and 12 because, contrary to the examiner's assertion, chloroform is not a pharmaceutically acceptable carrier. Each of claims 1 and 12 requires a composition comprising 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine together with a pharmaceutically acceptable carrier. Tomori is said to describe solutions of 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine in chloroform. Applicants respectfully submit that chloroform is not a pharmaceutically acceptable carrier within the meaning of claims 1 and 12 and that therefore Tomori fails to describe a pharmaceutical composition comprising 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine and a pharmaceutically acceptable carrier.

During examination, the claims are given their broadest reasonable interpretation, but that interpretation must be consistent with the meaning given in the specification. MPEP 2111. The interpretation must also be "consistent with the interpretation that those skilled in the art would reach." *Id.* citing *In re Cortright*, 165 F.3d 1353, 1359, 1468 (Fed. Cir. 1999). Further, the claims are interpreted from the point of view of "a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." MPEP 2111.01(III) quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). In addition, "[a]n applicant is entitled to be his or her own lexicographer and may rebut the presumption that claim terms are to be given their ordinary and customary meaning by clearly setting forth a definition of the term that is different from its ordinary and customary meaning(s)." MPEP 2111.01(IV) citing *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

From the rules of claim interpretation set forth above, the examiner will appreciate that claims 1 and 12 would have been anticipated by Tomori only if chloroform were considered a pharmaceutically acceptable carrier as of the filing date of the present application. This is because the claims are interpreted from the point of view of the person skilled in the art as of the effective filing date of the patent application. MPEP 2111.01(III). Tomori would not describe each and every element of the claims in issue (i.e. claims 1 and 12 of the present application) unless chloroform would be considered a pharmaceutically acceptable carrier as of the filing date of the present application.

The examiner cites U.S. Patent No. 4,025,528 (the '528 patent) column 17, lines 22-44 to support the assertion that chloroform is a pharmaceutically acceptable carrier. Applicants acknowledge that the '528 patent, column 17 lines 43-44 does appear to suggest that chloroform was regarded by the authors of the disclosure of that patent as a pharmaceutically acceptable carrier.

The '528 patent does not, however, reflect the meaning of "pharmaceutically acceptable carrier" that would have been given by the person skilled in the art in 2003, when

the present application was filed, and which is relevant to determining the patentability of claims 1 and 12. Applicants respectfully point out that the '528 patent was issued in 1977 and claims priority from an application that was filed in 1973. Therefore the statement in the '528 patent concerning the pharmaceutical acceptability of chloroform, if considered to reflect a general understanding of those skilled in the art that chloroform was a pharmaceutically acceptable carrier, would reflect such an understanding only as of approximately 1973, when the application which led to the '528 patent was originally written and not the meaning that would be given to the term "pharmaceutically acceptable carrier" at the time the present application was filed in 2003.

Applicants respectfully point out, notwithstanding the statements in the '528 patent, that chloroform was generally regarded as being pharmaceutically *unacceptable* at the time the present application was filed. As evidence thereof, applicants hereby submit copies of two 1976 publications in the Federal Register by the Food and Drug Administration (F.D.A.) concerning the pharmaceutical unacceptability of chloroform and also a copy of U.S. Patent 5,500,224 (the '224 patent).

In 1976, the F.D.A. banned the use of chloroform as an ingredient in human pharmaceutical and cosmetic products. The proposed regulations, published in 41 Fed. Reg. 15026 (April 9, 1976) cited a National Cancer Institute (N.C.I.) study which demonstrated the carcinogenicity of chloroform in animal studies, and which prompted the F.D.A. to propose the regulations banning the use of chloroform as an ingredient in human and drug cosmetic products. In analyzing the study, the F.D.A. Commissioner noted that "continued use of chloroform in human drug and cosmetic products may cause such products to be injurious to health and is therefore unwarranted. The Commissioner believes that it is in the interest of the public health ... to remove chloroform from human Food and Drug products." The F.D.A. subsequently published final regulations, published in 41 Fed. Reg. 26842 (June 29 1976), banning chloroform from drug and cosmetic products. Copies of these two Federal Register publications are provided for the examiner's reference.

Applicants respectfully submit that chloroform, a compound which is banned by law from use in human drug and cosmetic products because of its health risks, would not be regarded as a "pharmaceutically acceptable" carrier by the person skilled in the art. This is notwithstanding the possibility that chloroform might have been regarded as a pharmaceutically acceptable carrier in the past. As applicants pointed out above, it is the meaning of the terms used in the claims at the time of filing of the present application which must be considered when determining whether the claims of the present application are anticipated by a given reference.

As further evidence that chloroform was regarded as being pharmaceutically unacceptable at the time the present application was filed, applicants respectfully direct the examiner's attention to U.S. Patent 5,500,224 (the '224 patent). In column 2 lines 19-21, the '224 patent expressly states that chloroform is "pharmaceutically unacceptable" because of its high toxicity, thus contradicting the examiner's assertion that chloroform is a pharmaceutically acceptable carrier. The '224 patent is more probative evidence than the '528 patent of whether chloroform is "pharmaceutically acceptable" within the meaning of claims 1 and 12 of the present application, and whether the Tomori reference anticipates those claims, since the '224 patent dates from closer in time to the filing date present application than the '528 patent.

Applicants also respectfully point out that the examiner's assertion that chloroform is "pharmaceutically acceptable" carrier is inconsistent with the meaning of the term as it is used in the specification. The specification defines a "pharmaceutically acceptable carrier" as being a substance which is "not deleterious to the recipient". See p. 27 lines 11-13. Applicants respectfully point direct the examiner's attention to the Federal Register publications provided, where the F.D.A. Commissioner concluded that the use of chloroform in drug and cosmetic products posed a risk of cancer, an effect that applicants respectfully submit should be considered "deleterious". In fact, the F.D.A. final regulation banning the use of chloroform in cosmetic products expressly recognizes that chloroform is a

"deleterious substance". The applicable regulation, 21 C.F.R. § 700.18(a), published in 41 Fed. Reg. 26845 (June 29, 1976), states:

> 21 C.F.R. § 700.18. Use of chloroform as an ingredient in cosmetic products.
>
> (a) Chloroform has been used as an ingredient in cosmetic products. Recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats. Scientific literature indicates that chloroform is absorbed from the gastrointestinal tract, through the respiratory system, and through the skin. *The Commissioner concludes that, on the basis of these findings, chloroform is a deleterious substance which may render injurious to users any cosmetic product that contains chloroform as an ingredient.*

(emphasis added).

Applicants respectfully submit that the evidence submitted clearly demonstrates that chloroform would not have been considered a "pharmaceutically acceptable carrier" by the person skilled in the art at the time of filing of the present application, and that therefore the Tomori reference disclosing a solution of 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine in chloroform does not describe a pharmaceutical composition as claimed in claims 1 and 12. Reconsideration of the rejection of claims 1 and 12 under 35 U.S.C. § 102(b) is therefore respectfully requested.

(3) Rejection of Claims 2-11 under 35 U.S.C. § 103(a).

The examiner has rejected claims 1 and 12 under 35 U.S.C. § 103(a) as being allegedly unpatentable for obviousness over Tomori *et al. (J. Chromatog.* **1982**, *241*, 88-99) ("Tomori"). The applicants respectfully traverse.

The examiner states that the person skilled in the art with knowledge of the racemate as described in Tomori would have been motivated to separate the enantiomers to determine which of the two was more effective for the desired purpose, since enantiomers were allegedly known to possess a disproportionate amount of the desired biological activity.

It appears to the applicants that the rejection is based on the incorrect premise that a solution of 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine in chloroform is a "pharmaceutical composition" and that chloroform is a pharmaceutically acceptable carrier. The arguments presented to overcome the rejection of claims 1 and 12 as described above under 35 U.S.C. § 102(b) are therefore respectfully submitted as being effective to overcome the rejection of claims 2-11 under 35 U.S.C. § 103(a). Tomori fails to describe a pharmaceutical composition of racemic 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine, and therefore cannot be held to suggest to the person skilled in the art making a pharmaceutical composition of an enantiomer of 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine.

Further, it is not clear from the examiner's stated grounds of rejection for what purpose the person skilled in the art would allegedly have been motivated to separate the enantiomers of the tofisopam metabolite. It is respectfully pointed out that the examiner appears to have overlooked the fact that the Tomori reference fails to disclose a pharmaceutical utility of the tofisopam metabolite. Therefore, even assuming, arguendo, that a person of ordinary skill in the art with knowledge of a desirable biological activity of 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine would have had a reason to separate its enantiomers and make a pharmaceutical composition thereof, as suggested by the examiner, to determine which enantiomer had the desired activity, a person of ordinary skill in the art *not* knowing of any desirable biological activity of 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine would have had no reason to separate its enantiomers and make a pharmaceutical composition thereof. None of the references cited by the examiner in support of the rejection appear to reveal any desirable biological activity of 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine which might motivate the person of skill in the art to separate its enantiomers.

Based on the foregoing, reconsideration of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

(3) Rejection of Claims 1-6 for Alleged Obviousness Type Double Patenting.

The examiner has also rejected claims 1-6 for alleged obviousness-type double patenting over claim 5 of U.S. Patent No. 6,864,251 (the '251 patent), claim 5 of U.S. Patent Application Serial No. 10/309,573 (the '573 application), claim 13 of U.S. Patent Application Serial No. 10/727,940 (the '940 application) and claim 6 of U.S. Patent Application Serial No. 10/728,286 (the '286 application), each of which are said to claim methods of treatment using 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine. The examiner states that the claim to the pharmaceutical composition in the present application is an obvious variant of the claims to methods of treatment using the same compound in the patent and other applications.

Applicants respectfully point out that the rejection over the '573 application is duplicative of the rejection over the '251 patent since the '573 application is the application which resulted in the issuance of the '251 patent. Without acquiescing in the propriety of the rejection, applicants would be open to filing a terminal disclaimer to overcome the rejection should the examiner that the issue of alleged double patenting is the only outstanding issue as to the patentability rejected claims. The examiner is therefore respectfully requested to hold the matter of alleged double patenting in abeyance until the issues concerning the other grounds of rejection of the claims are resolved.

Applicants respectfully point out that the rejection for double patenting over claim 13 of the 940 application and claim 6 of the '286 application are premature since the allegedly conflicting claims in the co-pending applications have not yet been patented. The claims should therefore have been rejected only provisionally. Without acquiescing in the propriety of the rejection, applicants would be open to filing a terminal disclaimer should it be necessary to overcome the rejection as to the patentability of the rejected claims. The examiner is therefore respectfully requested to hold the matter of alleged double patenting in

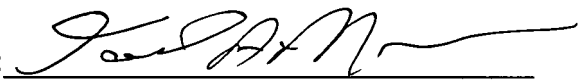
abeyance until the issues concerning the other grounds of rejection of the claims are resolved.

(4) Conclusion.

Based on the foregoing, applicants respectfully submit that the rejections under 35 U.S.C. §§ 102(b), 103(a) and 112 have been overcome. As indicated above, applicants are open to filing a terminal disclaimer, if required, in order to overcome the rejection of the claims that have rejected for double patenting. In addition, the applicants respectfully remind the examiner of the eligibility of the dependent process claims 13-40 for rejoinder under MPEP 821.04 when claim 1 is placed in condition for allowance.

Respectfully submitted

HERBERT W. HARRIS, *et al.*

BY: 

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proposed rules

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF AGRICULTURE

Rural Electrification Administration

[7 CFR Part 1701]

RURAL TELEPHONE PROGRAM

Proposed Revision of REA Standard for Acceptance Tests and Measurements of Telephone Plant

Notice is hereby given that, pursuant to the Rural Electrification Act, as amended (7 USC 901 et seq.), REA proposes to revise REA Bulletin 345–63 to announce a revision in REA Standard PC–4 for Acceptance Tests and Measurements of Telephone Plant. On issuance of REA Bulletin 345–63, Appendix A to Part 1701 will be modified accordingly.

Persons interested in the revised standard may submit written data, views or comments to the Director, Telephone Operations and Standards Division, Rural Electrification Administration, Room 1355, South Building, U.S. Department of Agriculture, Washington, D.C. 20250, on or before May 10, 1976. All written submissions made pursuant to this notice will be made available for public inspection at the Office of the Director, Telephone Operations and Standards Division during regular business hours.

A copy of the revised REA Standard PC–4 may be secured in person or by written request from the Director, Telephone Operations and Standards Division.

The text of revised REA Bulletin 345–63 announcing the revision of the standard is as follows:

REA BULLETIN 345–63

Subject: REA Standard for Acceptance Tests and Measurements of Telephone Plant.

I. *Purpose:* To announce issuance of a revised REA Standard PC–4 for Acceptance Tests and Measurements of Telephone Plant.

II. *General:* REA Standard PC–4 covers methods and procedures for conducting acceptance tests of REA borrowers' telephone plant. The actual tests required for any particular borrower's plant are specified in the latest revision of REA Form 511, if contract type construction is involved. This revision supersedes the current issue dated November 1970. The major changes include:

1. Addition of a section covering measurement of shield continuity.

2. Deletion of a numerical limit for total loop resistance unbalance.

3. Allowing the use of level tracing equipment for measurement of insertion loss and return loss.

4. Recommending the use of loop checking equipment for measurements of noise and insertion loss on subscribed loops.

5. A new format with the text and figures for each test or measurement as a unit for convenience of personnel making the measurements.

The revised standard becomes effective June 1, 1976. All testing done after that date shall comply in all respects with the revised REA Standard PC–4. This does not preclude the adoption of the revised standard prior to the effective date.

III. *Availability of Standard:* Copies of the revised PC–4 will be furnished by REA upon request. Questions concerning this revised standard may be referred to the Chief, Transmission Branch, Telephone Operations and Standards Division, Rural Electrification Administration, U.S. Department of Agriculture, Washington, D.C. 20250, telephone number 202 447–3917.

Dated: April 1, 1976.

C. R. BALLARD,
Assistant Administrator.

[FR Doc.76–9999 Filed 4–8–76;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 310 and 700]

[Docket No. 76N–0091]

CHLOROFORM AS AN INGREDIENT OF HUMAN DRUG AND COSMETIC PRODUCTS

Proposed Revision of Labeling Requirements

The Food and Drug Administration (FDA) is proposing to declare that any human drug product containing chloroform as an ingredient (active or inactive) is a new drug and deemed to be misbranded and that any cosmetic product containing chloroform as an ingredient is deemed to be adulterated. Interested persons have until May 10, 1976 to submit comments on this proposal. The Commissioner of Food and Drugs expects to issue final regulations based on the proposed regulations below to be effective by July 8, 1976.

EVIDENCE OF CARCINOGENICITY

On March 1, 1976, FDA received the National Cancer Institute's "Report On The Carcinogenesis Bioassay of Chloroform." The report presents a synopsis of results of a carcinogenesis bioassay of chloroform using mice and rats and concludes that chloroform induces liver cancer in mice and renal tumors in male rats. The summary of the report reads as follows:

A carcinogenesis bioassay of USP grade chloroform was conducted using Osborne-Mendel rats and B6C3F$_1$ mice. Chloroform was administered orally (by gavage) in corn oil to 50 animals of each sex and at two dose levels five times per week for 78 weeks. Rats were started on test at 52 days of age and sacrificed after 111 weeks. The dose levels for males were 90 to 180 milligrams per kilogram (mg/kg) body weight. Female rats were started at 125 and 250 mg/kg, reduced to 90 and 180 mg/kg after 22 weeks, with an average level of 100 and 200 mg/kg for the study. A decrease in survival rate and weight gain was evident for all treated groups. The most significant observation ($P=.0016$) was kidney epithelial tumors in male rats with incidences of: 0 percent in controls, 8 percent in the low-dose and 24 percent in the high-dose groups. Although an increase in thyroid tumors was also observed in treated female rats, this finding was not considered biologically significant. Mice were started on test at 35 days and sacrificed after 92 to 93 weeks. Initial dose levels were 100 and 200 mg/kg for males and 200 and 400 mg/kg for female mice. These levels were increased after 18 weeks to 150/300 and 250/500 mg/kg respectively so that the average levels were 138 and 277 mg/kg for males and 238 and 477 mg/kg for female mice. Survival rates and weight gains were comparable for all groups except high-dose females, which had a decreased survival. Highly significant increases ($P<.001$) in hepatocellular carcinoma were observed in both sexes of mice with incidences of: 98 percent and 95 percent for males and females at the high dose; 30 percent and 80 percent for males and females at the low dose as compared with 0 percent in both matched and colony control males, 0 percent in matched control females and 1 percent in colony control females. Nodular hyperplasia of the liver was observed in many low-dose male mice that had not developed hepatocellular carcinoma.

FDA has also received from the Cosmetic, Toiletry and Fragrance Association (CTFA), summaries of long term feeding studies, as well as several reports of the studies themselves, in which chloroform was administered, largely in the form of a dentifrice, to a variety of animal species. In one 96-week mouse study, 52 male and 52 female ICI mice each received 60 mg/kg of chloroform by gavage 6 days/week. After 80 weeks of treatment the male mice, but not the female mice, showed a greater incidence of renal tumors than found in the controls. In another study involving 4 different strains of mice, 52 male mice of each strain were intubated daily with 60 mg/kg of chloroform in a toothpaste. The duration of the studies for the C57BL and CBA strains of mice was 104 weeks, for CF/1, 93 weeks, and for ICI, 97 weeks. In the C57BL, CBA, and CF/1 strains of mice, chloroform did not increase the incidence of tumors; however, in the ICI mice there was a positive ro-

lationship between the administration of chloroform and the incidence of renal tumors. Such evidence of renal tumors in male ICI mice given 60 mg/kg/day of chloroform was reproducible in a second study. In one 95-week oral study in rats, 50 male and 50 female Sprague-Dawley SPF rats received 60 mg/kg of chloroform in the form of a toothpaste delivered by gavage 6 days/week. This study did not indicate that chloroform is carcinogenic to rats. New data submitted by the CTFA to FDA's OTC Oral Cavity Products Review Panel included a summary of studies on dogs for 7 years. In these studies, chloroform was administered in a toothpaste to 32 beagles; 8 males and 8 females were given chloroform at a dose level of 15 mg/kg/day and 8 males and 8 females were given chloroform at a dose level of 30 mg/kg/day. The results were that the treated dogs did not develop an excess of tumors at any site as compared with the controls.

The CTFA reported that human studies were also conducted with dentifrices and mouthwashes containing chloroform. The human studies, which tested the effect of a dentifrice and a mouthwash upon oral tissues when used in a normal manner, included evaluation of blood enzyme and urea levels.: No evidence of adverse effect upon liver function, as measured by these clinical tests, was reported.

PETITION TO BAN CHLOROFORM

In a letter dated December 30, 1975, the Health Research Group (HRG), 2000 P St. NW., Washington, D.C. 20036, requested that the Commissioner immediately ban the use of chloroform in all products under FDA's jurisdiction, require that manufacturers recall from the market all products that contain chloroform, and warn consumers and doctors against the use of such products. In support of this request, HRG cited the then still unreported study of the National Cancer Institute and a monograph on chloroform published by the International Agency for Research on Cancer ("IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man," Vol. I, pp. 61–65, 1972). The IARC monograph reported that the frequency of liver tumors was high in certain animal studies conducted in 1945 and 1967 on the carcinogenicity of chloroform; the monograph stated, however, that an assessment of the carcinogenicity of chloroform awaits further experimental evidence.

Copies of the National Cancer Institute's report, the IARC monograph, reports of rat, mouse, beagle and human studies submitted by CTFA, data submitted to FDA's OTC Oral Cavity Products Review Panel, and HRG's petition have been placed on public display at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, and may be seen Monday through Friday from 9 am to 4 pm except on Federal legal holidays.

COMMISSIONER'S ANALYSIS

The Commissioner has reviewed the report of the National Cancer Institute and has considered the data submitted by CTFA. Although he is not aware of any direct evidence that chloroform induces cancer in man, the Commissioner recognizes that the positive finding of cancer in test animals in the National Cancer Institute report indicates chloroform may pose a risk of cancer for humans. Experience has indicated that, with one or two possible exceptions, compounds that are carcinogenic in humans are also carcinogenic in one or more experimental animal bioassay systems. In addition, several compounds first detected as a carcinogen in experimental animals were later found to cause human cancer. The clear demonstration that a compound is carcinogenic in experimental animals must, therefore, be taken as evidence that it has the potential for carcinogenesis in humans unless there is strong evidence to the contrary.

On the other hand, negative evidence in experimental animals, such as reported in some of the studies submitted by CTFA, does not exclude the potential human carcinogenicity of a substance. The Commissioner is of the opinion that the risk to humans through frequent and long-term exposure to a substance in human drugs and cosmetics that has been shown to be an animal carcinogen is contrary to the public health unless the benefit of such exposure clearly outweighs the risk. Any benefits attributed to the use of chloroform in human drug products are outweighed by the risks, particularly in view of the availability of safe and suitable alternative ingredients. The lack of any benefit related to the use of chloroform in cosmetic products clearly does not warrant any risk. The Commissioner is therefore proposing to determine that continued use of chloroform in human drug and cosmetic products may cause such products to be injurious to health and is therefore unwarranted. The Commissioner believes that it is in the interest of the public health and prudent consumer protection to remove chloroform from human drug and cosmetic products.

Elsewhere in this issue of the FEDERAL REGISTER the Commissioner is proposing to revoke approvals of the use of chloroform as a food additive. The Commissioner will issue in the FEDERAL REGISTER in the near future a notice concerning the use of chloroform in products intended for use in or on animals other than man.

The Commissioner is proposing that any human drug product containing chloroform as an ingredient (active or inactive) is a new drug and deemed to be misbranded within the meaning of sections 201(p) and 502 of the act, respectively (21 U.S.C. 321(p) and 352). The Commissioner also proposes to declare that chloroform is a deleterious substance. Any cosmetic product that contains chloroform as an ingredient would thus be deemed to be adulterated under section 601(a) of the Act (21 U.S.C. 361(a)).

Chloroform has been used as an ingredient in products such as cough preparations, liniments, and toothpastes for many decades. Data available to FDA indicate that approximately 95 percent of all orally administered drug products containing chloroform contain a concentration of 1 percent or less. Higher contrations are present largely in certain brands of toothpaste and in topical preparations from which the systemic absorption of chloroform is incomplete. The amount of chloroform to which any individual might be exposed from these sources is, on a mg/kg/day basis, only a small fraction of the dose administered to the rats and mice in the NCI studies. Moreover, almost all exposures of humans to any particular human drug and cosmetic product containing chloroform are likely to be short term by comparison with the lifetime exposure to chloroform of the rats and mice in the NCI studies. Because there are no data to show that chloroform is a human carcinogen and in view of the small amount of chloroform to which any individual might be exposed in using currently marketed chloroform-containing human drug and cosmetic products, the Commissioner ahs determined that the present risk to the public is so minimal that it cannot reasonably be considered an imminent health hazard.

The agency has considered in detail the best approach to assuring that drug and cosmetic products on the market do not contain chloroform. Because of the wide distribution of a large number of drug and cosmetic products containing chloroform, immediate removal of such products is considered impracticable and the enforcement to assure the effectiveness of a recall does not justify the diversion of agency resources in view of the minimal risk of those products to the public health. The Commissioner believes that a prompt but orderly replacement of all drug and cosmetic formulations containing chloroform represents the more responsible approach. The Commissioner encourages industry to replace chloroform-containing products with reformulated products as soon as possible. He advises that FDA will not regard any removal from the market as a recall requiring the manufacturers to notify FDA of such action.

The Commissioner has compiled, through a search of the files, a list of human drug products known to contain chloroform as either an active or inactive ingredient. A copy of the list has been placed on file in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, and may be seen, Monday through Friday, from 9 am to 4 pm, except on Federal legal holidays. Copies of the list may be obtained through a written request to the Public Records and Documents Center pursuant to the Freedom of Information Act. The anticipated cost for the list is $6.00 per copy.

CONCLUSIONS

The Commissioner is taking the following actions: He is proposing two new regulations, §§ 310.513 and 700.18 (21 CFR 310.513 and 700.18), declaring that any human drug product containing chloroform as an ingredient is a new drug and

deemed to be misbranded and that any cosmetic product containing chloroform as an ingredient is deemed to be adulterated. Interested persons have until May 10, 1976 to submit comments. The Commissioner will not entertain any request for extension of the comment period. Moreover, unless comments on the proposal raise substantial issues that cannot be immediately resolved, the Commissioner intends to issue final regulations by June 8, 1976. The Commissioner proposes that the final regulations would be effective 30 days after publication, which would be on or about July 8, 1976. After this date, any human drug product containing chloroform that is introduced or delivered for introduction into interstate commerce by a manufacturer, repacker, relabeler, or own label distributor would be regarded as a new drug or deemed to be misbranded, or both, and would be subject to regulatory action under sections 301, 502, and 505 of the Federal Food, Drug, and Cosmetic Act. Likewise, after this date, any cosmetic product containing chloroform as an ingredient that is introduced or delivered for introduction into interstate commerce by a manufacturer, repacker, relabeler, or own label distributor would be deemed to be adulterated under section 601(a) of the act and subject to regulatory action. The agency will conduct an appropriate surveillance program to assure compliance with this regulation.

In § 310.513, the Commissioner is proposing that any current holder of an approved new drug application for a drug product containing chloroform as an ingredient shall submit to FDA on or before July 8, 1976 a supplemental application providing for a revised formulation removing chloroform as an ingredient. He is of the opinion that chloroform in amounts greater than one percent would generally be present in a drug product as an active ingredient and the removal of or substitution for chloroform in such products may affect the product's integrity and effectiveness. Therefore, under the proposal, if the drug product presently marketed contains more than one percent chloroform, the revised formulation may not be marketed before the receipt of written notice of approval of the supplemental application by FDA. If the drug product presently marketed contains one percent or less chloroform, the revised formulation may be marketed after submission of the supplemental application but before the receipt of written notice of its approval by FDA.

Under proposed § 310.513(d), any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND notice) for a drug product containing chloroform as an ingredient shall amend the IND notice on or before July 8, 1976 to revise the formulation removing chloroform as an ingredient.

The Commissioner, under proposed § 310.513(e), would initiate action to withdraw approval of an application or terminate an IND notice if any current holder of an approved new drug application or sponsor of an IND notice fails to submit a supplemental application or to amend an IND notice as set forth, and within the time periods provided for, in § 310.513.

Reformulation to remove chloroform from a drug product that is not now subject to requirements for an approved new drug application may occur without prior agency approval regardless of chloroform content. Manufacturers should be advised, however, that the reformulation of such products may in some cases, as where the percent of chloroform content is significant, affect the product's present legal status under the act. Inquiries about the new drug status of any reformulation may be directed in writing to the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD-310), 5600 Fishers Lane, Rockville, MD 20852.

The Commissioner encourages all manufacturers of human drug or cosmetic products containing chloroform to revise their formulations and remove chloroform as soon as possible and in advance of the publication of the final regulation. He advises that FDA will not take regulatory action if a current holder of an approved new drug application or sponsor of an IND notice acts to comply with the proposed regulations before issuance of the final regulations. The Commissioner advises, however, that before the holder of an approved new drug application can market the revised formulation, the holder must submit a supplemental application and, if the product currently marketed contains more than one percent chloroform, obtain approval of the supplemental application by FDA.

The scientific literature indicates that chloroform is absorbed from the gastrointestinal tract, through the respiratory system, and through the skin, and therefore the proposed regulations regarding the use of chloroform as an ingredient in human drug and cosmetic products would be applicable to all forms of such products regardless of the route of administration or method of application. The Commissioner is not aware of any licensed biological product that contains chloroform as an ingredient. Accordingly, amendment of the biologics regulations is not proposed at this time.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. The Commissioner has also carefully considered the inflation impact of the proposed regulation as required by Executive Order 11821, OMB Circular A-107, and interim guidelines issued April 1, 1975 by the Department of Health, Education, and Welfare, and no major inflation impact has been found. Copies of the FDA environmental and inflation impact assessments are on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 301, 502, 505, 601(a), 701(a), 52 Stat. 1042–1043, 1050–1055, as amended (21 U.S.C. 331, 352, 355, 361(a), 371(a))) and under authority delegated to the Commissioner (21 CFR 2.120), it is proposed that Parts 310 and 700 be amended as follows:

1. In Part 310, by adding a new § 310.513 to read as follows:

§ 310.513 Chloroform, use as an ingredient (active or inactive) in drug products.

(a) Chloroform has been used as an ingredient in drug products, such as cough preparations, liniments, and toothpastes. Although considered safe for many years, recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats.

(b) Any drug product containing chloroform as an ingredient is a new drug within the meaning of section 201 (p) of the act and deemed to be misbranded and is subject to regulatory action under sections 301, 502, and 505 of the act.

(c) Any holder of an approved new drug application for a drug product containing chloroform as an ingredient shall submit to the Food and Drug Administration on or before July 8, 1976 a supplemental application providing for a revised formulation removing chloroform as an ingredient.

(1) The supplemental application shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) The date that the composition of the drug product will be changed.

(iii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iv) Data available to establish the stability of the revised formulation and, if the data are too limited to support a conclusion that the drug will retain its declared potency for a reasonable marketing period, a commitment from the applicant:

(a) To test the stability of marketed batches at reasonable intervals;

(b) To submit the data as they become available; and

(c) To recall from the market any batch found to fall outside the approved specifications for the drug.

(v) Copies of the label and all other labeling to be used for the drug product (a total of 12 copies if in final printed form, 4 copies if in draft form).

(2) If such drug product now contains more than one percent chloroform, the revised formulation containing no chloroform shall not be marketed before the receipt of written notice of approval of the supplemental application by the Food and Drug Administration.

(3) If such drug product now contains one percent or less chloroform, the revised formulation containing no chloroform may be marketed after submission of the supplemental application but prior to the receipt of written notice of its approval by the Food and Drug Administration.

(d) Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND notice) for a drug product containing chloroform as an ingredient shall amend the IND notice on or before July 8, 1976 to revise the formulation removing chloroform as an ingredient.

(e) The Commissioner will initiate action to withdraw approval of an application or terminate an IND notice in accordance with the applicable provisions of section 505 of the act and Parts 312 and 314 of this chapter upon failure of a holder of an approved new drug application or sponsor of an IND notice to comply with the provisions of paragraph (c) or (d) of this section.

2. In Part 700, by adding new § 700.18 to read as follows:

§ 700.18 Use of chloroform as an ingredient in cosmetic products.

(a) Chloroform has been used as an ingredient in cosmetic products. Recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats. Scientific literature indicates that chloroform is absorbed from the gastrointestinal tract, through the respiratory system, and through the skin. The Commissioner concludes that, on the basis of these findings, chloroform is a deleterious substance which may render injurious to users any cosmetic product that contains chloroform as an ingredient.

(b) Any cosmetic product containing chloroform as an ingredient is deemed to be adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act.

Interested persons may, on or before May 10, 1976, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, written comments regarding this proposal. Comments should be in quintuplicate (except that individuals may submit single copies) and should be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Unless these comments raise substantial issues that cannot be immediately resolved, the Commissioner intends to issue a final regulation before June 8, 1976. This final regulation would be effective July 8, 1976. Received comments may be seen in the above office, Monday through Friday, from 9 am to 4 pm, except on Federal legal holidays.

Dated: April 5, 1976.

A. M. Schmidt,
Commissioner of Food and Drugs.

[FR Doc.76-10253 Filed 4-8-76;8:45 am]

[21 CFR Part 121]

[Docket No. 76N-0097]

CHLOROFORM IN CONTACT WITH FOOD

Proposal To Amend Food Additive Regulation

The Food and Drug Administration (FDA) is proposing to amend the food additive regulations in § 121.2520 *Adhesives* (21 CFR 121.2520) and in § 121.2574 *Polycarbonate resins* (21 CFR 121.2574) by deleting "chloroform" from lists of substances contained in these regulations, and in § 121.106 *Substances prohibited from use in human food* by listing chloroform therein. The Commissioner of Food and Drugs expects to issue final regulations based on the proposals described below no later than July 8, 1976, which shall be effective upon publication. Interested persons have until May 10, 1976 to submit comments on the proposal.

Sections 121.2520 and 121.2574 provide for the use of chloroform as a component of certain food-contact articles (food-packaging adhesives and polycarbonate resins) under certain prescribed conditions. The only other permitted use of chloroform in or on food is the exemption from the requirements for a pesticide tolerance established by the Environmental Protection Agency in § 180.1001 (40 CFR 180.1001); the agency has been notified of this proposed rule.

On March 1, 1976, FDA received the National Cancer Institute's "Report on the Carcinogenesis Bioassay of Chloroform." The report presents a synopsis of the results of a carcinogenesis bioassay of chloroform using mice and rats, and concludes that chloroform induces liver cancer in mice and renal tumors in male rats. (A summary of the report appears in an FDA proposal concerning chloroform in human drugs and cosmetics, published elsewhere in this issue of the FEDERAL REGISTER.)

FDA has also received from the Cosmetic, Toiletry and Fragrance Association (CTFA), summaries of long-term feeding studies, as well as several reports of the studies themselves, in which chloroform was administered, principally in the form of a dentrifice, to a variety of animal species. These studies were conducted in rats and mice with the chloroform administered at a dosage level of 60 milligrams per kilogram (mg/kg) of body weight, and in beagles with the chloroform administered at dosage levels of 15 mg and 30 mg of body weight. The results reported for these studies did not indicate chloroform to be carcinogenic in rats or beagles. For mice, there was evidence of the production of kidney neoplasms in male mice of one of the four mouse strains tested. (A more detailed description of the studies appears in the FDA proposal concerning chloroform in drugs and cosmetics, published elsewhere in this issue of the FEDERAL REGISTER).

The CTFA reported that human studies were also conducted with dentifrices and mouthwashes containing chloroform. The human studies, which tested the effect of a dentifrice and a mouthwash upon oral tissues when used in a normal manner, included evaluation of blood enzyme and urea levels. No evidence of adverse effect upon liver function, as measured by these clinical tests, was reported.

In a petition dated December 30, 1975, the Health Research Group (HRG), 2000 P St. NW., Washington, DC 20036, requested that the Commissioner immediately ban the use of chloroform in all products under FDA's jurisdiction, require that manufacturers recall from the market all products that contain chloroform, and warn consumers and doctors against the use of such products. In support of this request, HRG cited the then still unreported study of the National Cancer Institute and a monograph on chloroform published by the International Agency for Research on Cancer ("IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man," Vol. I, pp. 61 through 65, 1972). The IARC monograph reported that the frequency of liver tumors was high in certain animal studies conducted in 1945 and 1967 on the carcinogenicity of chloroform; the monograph stated, however, that an assessment of the carcinogenicity of chloroform awaited further experimental evidence.

Copies of the National Cancer Institute's report, the IARC monograph, reports of rat, mouse, beagle and human studies submitted by CTFA, data submitted to the FDA OTC Oral Cavity Products Review Panel, and HRG's petition have been placed on public display at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, and may be seen Monday through Friday from 9 am to 4 pm except on Federal legal holidays.

Having evaluated the available data, the Commissioner concludes that the National Cancer Institute report demonstrates that chloroform is a carcinogen in test animals. Accordingly, under the provisions of section 409(c)(3)(A) of the act, which is known as the Delaney clause (21 USC 348 (c)(3)(A)), its use as a food additive may no longer be approved. The Commissioner therefore proposes to amend the food additive regulations to delete provisions for use of chloroform as a component of food-contact articles, and to list the item as a substance prohibited from use in human food. The Commissioner expects to issue the final regulation prohibiting the use of chloroform as a food additive (directly or in-

directly) no later than July 8, 1976, which shall be effective upon publication under section 409(e) of the act (21 USC 348(e)).

The Commissioner advises that he is not aware of any data to show that chloroform is a human carcinogen. Additionally, he advises that only small amounts of chloroform remain in adhesives or polycarbonate resins from its use as a solvent. Furthermore, only a vanishingly small amount of this chloroform could migrate into food from these food-contact articles. Therefore, the Commissioner concludes that the potential risk to the public health is not sufficient to require removal from the market of food-contact articles containing chloroform or the issuance of a public warning against the use of these products. Consequently, the Commissioner is of the opinion that the public health would be adequately served by permitting the use of existing stocks of products containing chloroform that were manufactured prior to the effective date of the final regulation but prohibiting any future use of chloroform as a food additive.

Elsewhere in this issue of the FEDERAL REGISTER, FDA is proposing to declare that any human drug product containing chloroform as an ingredient is a new drug and deemed to be misbranded, and that any cosmetic product containing chloroform as an ingredient is deemed to be adulterated.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. The Commissioner has also carefully considered the inflation impact of the proposed regulation as required by Executive Order 11821; OMB Circular A-107, and interim guidelines issued April 1, 1975 by the Department of Health, Education, and Welfare, and no major inflation impact has been found. Copies of the FDA environmental and inflation impact assessments are on file with the Hearing Clerk, Fod and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 402, 409, 701, 52 Stat. 1042, 1046–1047 as amended, 1049, 1055–1056, 72 Stat. 1784–1787 (21 USC 321(s), 342, 348, 371)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes to amend Part 121, as follows:

1. In § 121.106 by adding new paragraph (e) (5) to read as follows:

§ 121.106 Substances prohibited from use in human food.

* * * * * *

(e) * * *

(5) *Chloroform* (trichloromethane) $CHCl_3$. (i) Chloroform is a synthetic chemical which has been used as a solvent for the extraction and purification of varied chemicals and polymers in the manufacture of food-contact articles.

(ii) Food containing any added chloroform is deemed to be adulterated in violation of the act based upon a regulation published in the FEDERAL REGISTER of April 9, 1976.

§ 121.2520 [Amended]

2. In § 121.2520 *Adhesives* by deleting from paragraph (c) (5) the item "chloroform" from the list of substances therein.

§ 121.2574 [Amended]

3. In § 121.2574 *Polycarbon resins* by deleting the item "chloroform" from the list of substances therein.

Interested persons may, on or before May 10, 1976, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: April 5, 1976.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.76-10252 Filed 4-8-76;8:45 am]

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Federal Insurance Administration

[24 CFR Part 1917]

[Docket No. FI-994]

CHESAPEAKE, VIRGINIA

Appeals From Flood Elevation Determination and Judicial Review

The Federal Insurance Administrator, in accordance with Section 110 of the Flood Disaster Protection Act of 1973 (P.L. 93-234), 87 Stat. 980, which added Section 1363 to the National Flood Insurance Act of 1968 (Title XIII of the Housing and Urban Development Act of 1968 P.L. 90-448), 42 U.S.C. 4001-4128, and 24 CFR Part 1917 (Section 1917.4 (a)) hereby gives notice of his proposed determinations of flood elevations for the City of Chesapeake, Virginia.

Under these Acts, the Administrator, to whom the Secretary has delegated the statutory authority, must develop criteria for flood plain management in identified flood hazard areas. In order to participate in the National Flood Insurance Program, the City must adopt flood plain management measures that are consistent with the flood elevations determined by the Secretary.

Proposed flood elevations (100-year flood) are listed below for selected locations. Maps and other information showing the detailed outlines of the flood-prone areas and the proposed flood elevations are available for review at the Library, Chesapeake, Virginia.

Any person having knowledge, information, or wishing to make a comment

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER D—DRUGS FOR HUMAN USE

SUBCHAPTER G—COSMETICS

[Docket No. 76N-0091]

PART 310—NEW DRUGS

PART 700—GENERAL

Chloroform as an Ingredient of Human Drug and Cosmetic Products

The Food and Drug Administration (FDA) is issuing final regulations declaring that any human drug product containing chloroform as an ingredient (active or inactive) is a new drug and is misbranded, and any cosmetic product containing chloroform as an ingredient is adulterated. These final regulations are effective July 29, 1976. Therefore, after July 29, 1976, any human drug or cosmetic product containing chloroform that is introduced or delivered for introduction into interstate commerce will be subject to regulatory action.

These regulations are based on a notice published in the FEDERAL REGISTER of April 9, 1976 (41 FR 15026) in which the Commissioner of Food and Drugs proposed to prohibit the continued use of chloroform as an ingredient of human drug and cosmetic products. Interested persons were invited to submit comments on the proposal on or before May 10, 1976.

The final regulations are essentially the same as those proposed, and require any holder of an approved new drug application (NDA), or any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND), for a drug product containing chloroform as an ingredient, to submit a supplemental application or amend his IND to provide for a revised formulation removing chloroform as an ingredient. If a drug product now contains more than 1 percent chloroform, the revised formulation containing no chloroform may not be marketed before the receipt of written notice of approval of the supplemental application by FDA. If a drug product now contains 1 percent or less chloroform, the revised formulation containing no chloroform may be marketed after submission of a supplemental application but prior to the receipt of written notice of its approval by FDA. Failure to submit a supplemental application or to amend an IND notice in accordance with this regulation would be grounds for withdrawal of approval of an application or termination of an IND notice.

As stated in the preamble to the proposal, reformulation to remove chloroform from a drug product that is not now subject to requirements for an approved NDA may occur without prior agency approval regardless of chloroform content. Reformulation of such products may in some cases, as where the percent of chloroform content is significant, affect the product's present legal status under the Federal Food, Drug, and Cosmetic Act. Inquiries concerning the new drug status of any reformulation may be directed in writing to the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD-310), 5600 Fishers Lane, Rockville, MD 20852.

The Commissioner advises that reformulation of a human drug product to remove chloroform as an active or inactive ingredient constitutes a "material change" as defined in § 207.3(g) (21 CFR 207.3(g)) requiring the assignment of a new National Drug Code (NDC) number in accordance with § 207.35(b)(4) (21 CFR 207.35(b)(4)). Section 207.35(b)(4) requires that a new NDC number shall be assigned whenever any material change occurs in product characteristics. The term "any material change" is defined in § 207.3(g) to include, among other things, any change in the quantity or identity of the active ingredients, any significant change in the labeling of a prescription drug, and any significant change in the label of an OTC drug. Therefore, since section 502(e)(1)(A)(ii) of the act (21 U.S.C. 352(e)(1)(A)(ii) requires that the label of all chloroform-containing drug products bear the quantity or proportion of chloroform, whether active or inactive, the removal of chloroform from the formulation of such a product would necessitate a change in the label. Further, removal of chloroform from a formulation as an active ingredient would affect a product's characteristics. It is therefore clear that reformulation of a chloroform-containing drug product to remove chloroform meets the definition of "any material change" in § 207.3(g) thereby requiring a new NDC number in accordance with § 207.35(b)(4).

In response to the proposal, comments were received from manufacturers, a physician, a State consumer affairs unit, a professional association, trade associations, and individuals. Several comments contained specific requests for revisions or clarification of the regulation. A summary of the significant comments and the Commissioner's conclusions are as follows:

1. One comment from the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), which also submitted safety data to FDA on studies involving the use of chloroform, questions the relevancy, design, execution, and interpretation of the National Cancer Institute (NCI) studies, and expressed the opinion that it is scientifically unjustified to disregard CTFA's studies in favor of the NCI studies. The specific points raised by the comment in opposing the Commissioner's determination that chloroform is a carcinogen or is otherwise a deleterious substance are as follows:

a. The comment contends that the NCI studies in no way consider the differences in metabolism between rodents and man. In support of this contention regarding differences in metabolism, the comment cites an article by Hill et al., "Genetic Control of Chloroform Toxicity in Mice," *Science*, 190:159, 1975; a recent review by Charlesworth in *BIBRA* (British Industrial Biological Research Association) *Information Bulletin*, 14:225, 1975, which cites Taylor et al. in *Xenobiotica*, 4:165, 1974; and a paper entitled "Covalent Binding of Haloalkanes to Liver Constituents, but Absence of Mutagenicity on Bacteria in a Metabolizing Test System" by Uehleke, Greim, Kramer and Werner, presented at the fifth meeting of the European Environmental Mutagen Society, Florence, October 19–22, 1975. The comment states that (1) Hill et al. demonstrated that there are genetic factors in mice that affect susceptibility to chloroform lethality and induction of organ pathology and that these are associated with a metabolite whose formation is regulated by genetic factors; (2) Charlesworth reported distinct species differences to show that the metabolic fate of chloroform in mice, and most likely in rats, is not the same as in man, that there are sex-linked differences in metabolism that are peculiar to the mouse, and that man appears to eliminate more of the chloroform unchanged in the exhaled air; (3) Taylor et al. concluded that the mouse is an unsuitable species for evaluating the toxic effects of chloroform; and (4) Uehleke found in the "Ames study" that chloroform is not mutagenic and unlikely to be carcinogenic.

The comment further states that a "recognized international expert in oncology" concluded that, in consideration of the findings in the NCI report and those obtained by himself, "there is obviously wide species, strain, and sex variation both in the incidence of spontaneous tumor of the liver and kidney and in the response of these organs to chloroform." The comment claims that such a conclusion is supported by an opinion expressed by Dr. Grasso in a talk entitled "Evaluation of the Hepatoma in the Rodent in Carcinogenesis Bioassay" summarized in *BIBRA*, 1975 ("The Value of the Mouse in Carcinogenicity Testing"), in which he stated that there is considerable disagreement on the diagnosis of hepatic nodular lesions.

The Commissioner views the conclusions expressed in the comment as relying on the finding that, in studies of three mouse strains, male and female mice showed a sex-linked difference in ability to metabolize choloroform. The Commissioner does not agree that this forms an adequate basis for rejecting the mouse as a useful experimental animal, especially since the work of Hill et al. indicates that this variability exists not only between sexes but also within the same sex among different strains of the same species. Since these authors cite findings in humans of large interindividual differences in the disposition of commonly used drugs—differences which they attribute to genetic variability—it is not surprising that chloroform toxicity would be variable in the same species as well.

The Commissioner points out that the NCI report observes the variation in species and sex in the incidence of spontaneous tumor of the liver and kidney, and the response of these organs to chloroform. The report notes that the Osborne-Mendel strain was selected by

NCI because it was reported to be sensitive to the carcinogenic effects of carbon tetrachloride (CCl_4). The question of genetic drift within a strain might also be a factor since the positive control (CCl_4) produced a relatively low response (<5 percent with hepatocellular carcinomas). Thus, if anything, the Osborne-Mendel rats used in the NCI studies appear to be less sensitive to the heptaocarcinogen than those reported in the literature.

The Commissioner recognizes that there is disagreement among pathologists on diagnosis of lesions, including hepatic nodular lesions. However, proliferative changes and neoplastic lesions are discussed in considerable detail on pages 32–37 and 40 of the NCI report. The critique submitted by the comment provides no new information that would negate the effects discussed in the pathology section of the NCI report.

Regarding the reported findings of Uehleke in the "Ames study," which used a bacterial system, the Commissioner recognizes that rapid progress is being made in the development of mutagenicity test systems. He is aware of a number of reports indicating a mutagenicity-carcinogenicity correlation using these test systems. However, a number of "false positives" as well as "false negatives" have been observed in these test systems. Such tests using nonmammalian systems have not been validated for establishing correlations and are not considered an appropriate basis for regulatory actions.

b. The comment also argues that the dosage in the NCI studies was excessive and thus does not support the contention of risk to humans. Noting that the NCI report states that the methodology used in their studies differs from that which is currently used by NCI, the comment states that the most serious defects in the methodology used are the inadequacy of the subchronic toxicity study to determine the maximal tolerated dose (MTD) and one-half MTD, and the failure to employ a meaningful definition of MTD. The comment further states that had a proper and reliable subchronic study been conducted, employing liver and renal function measurements as well as histological assessment of the effects of chloroform upon the liver and kidney, it would have been found that the dose levels used were too toxic. In support, the comment notes that in the NCI rat study, the dose levels had to be reduced after 22 weeks of treatment because the lethal consequences were too great. The comment also cites in support a short term study conducted at Bio/dynamics Inc. at dosage levels of 60, 120, 240, and 480 milligrams/kilogram and with the same strain of mice as that used in the NCI study. In the Bio/dynamics Inc. study both males and females had poor tolerance to the chloroform and at the 480 and 240 milligrams/kilogram levels most of the mice died.

It is the Commissioner's opinion that the growth and survival curves as plotted for the mice in the NCI report reveal no significant effect on growth from the dosages administered, and only in the high-dose-level female mice is there an effect seen on survival. However, this effect was observed late in the study, when the death rate showed a sudden increase after the 70th week. The Commissioner therefore concludes that the dosages in the NCI mouse study conform to the standards generally accepted for an MTD to be used in carcinogenicity studies.

In the NCI rat study, it is true that the survival rate for chloroform-treated rats was lower than that for control rats. However, in the Commissioner's view the high dosage level for male rats appears to conform to standards for MTD when the first 90 days of the growth curves are examined. The comment's objection regarding excessive dosage (> MTD) would apply only to female rats. In this regard the Commissioner notes that the statement in the comment that dosage levels employed had to be reduced after 22 weeks because of lethality applies only to the female rats. Despite the reduction in dosage, the survival curves show a consistently lower survival rate. However, the Commissioner emphasizes that there was no increase in tumors reported for these animals. Rather, it was only in the male rats that an increased incidence of renal tumors was reported.

The comment also points out that the ratio of tumor-bearing animals to animals involved in all chloroform treatment groups is less than that found in both male and female matched control groups. This observation, however, is noted and described by NCI in their report as not significant. Moreover, the Commissioner believes the distribution of other than kidney tumors to be normal. Aside from this, the comment disregards the dose-related time of tumor onset. The CTRA analysis further states that "• • • data for the female groups indicate that chloroform treatment may have actually exerted beneficial effects." Obviously, the lethal effects cannot be viewed as beneficial. Finally, the Commissioner notes that in the case of male rats, where dosage would appear to conform to the generally accepted standards for carcinogenicity studies, definite evidence of kidney carcinogenicity appeared.

It is the Commissioner's view that the study conducted by Bio/dynamics Inc. was one of expediency and that the report was hastily prepared. The report indicates that the animals used were not of comparable age and weight as those used in the NCI study, there are apparent inconsistencies in some of the data tables, and the supplier of the mice for the Bio/dynamics Inc. study was different from that for the NCI study. The health of the mice is also questionable. Through communications with NCI, the Commissioner has been advised that the colony of mice of the supplier of Bio/dynamics Inc. showed pinworm infestations and high hepatitis virus titers. The CTFA representative was advised of this problem before its study was performed. In addition, the period of adaptation and quarantine appears to be inadequate since the mice were shipped 5 days prior to the administration of chloroform.

In response to the reported intolerance and the high mortality rate reported by the Bio/dynamics Inc. study, the NCI investigators administered dosages of 100, 200, 300, and 400 milligrams/kilogram of chloroform to groups of mice for 14 days. No deaths were observed for any group during this period. To produce lethality, dosages of 3620 and 5000 milligrams/kilogram were administered to these animals. Thus, except as stated above, the Commissioner cannot explain the results of the Bio/dynamics Inc. study. However, he recognizes that disparities in results may be due to variations in environmental, technical, and other experimental factors.

c. The comment also questions the bases for selecting the colony controls in the NCI study. It expresses the opinion that the NCI conducted the study with insufficient controls, citing the chloroform-matched colony group as an example, and then stacked the numbers by culling controls from other studies. The comment states that the so-called controls were not housed in the same room nor were they put on the study simultaneously with the treated and matched colony groups. Further, it cites as objectionable that animals that received other volatile agents, among which was carbon tetrachloride, were housed in the same room with the animals receiving chloroform.

The NCI report recognizes that the number of matched controls was less than that used in its current bioassay program. Despite this limitation, the induction of hepatocellular carcinoma in mice was highly significant, and the report concludes that this bioassay was a valid test for carcinogenic effect. The Commissioner rejects the charge of "culling" or "stacking." The NCI study incorporated colony controls of the same strain and source, maintained in the same room and in the same manner as the chloroform "matched" controls in the mouse-study analysis. The influence of other chemicals being tested in the same room is discussed extensively in the NCI report, on pages 41–43. These limitations were recognized and considered; in the Commissioner's view, they do not call into question the results of the NCI study.

d. The comment argues that the extraordinarily high doses of chloroform used in the NCI study may show that hepatocellular carcinoma in mice was secondary to the liver-necrotizing effect of chloroform. The comment points to FDA action on selenium published in the FEDERAL REGISTER of April 27, 1973 (38 FR 10458) and January 8, 1974 (39 FR 1355) and states that selenium was determined not to be a carcinogen for this very reason.

The Commissioner advises that he is not aware of any data supporting the secondary carcinogenesis argument regarding chloroform forwarded by the comment, nor do any data submitted to FDA by CTFA support such an argument. Further, experts in the field of liver car-

cinogenesis today do not regard necrosis as sufficient cause for tumor induction.

e. The comment contends that FDA has never made a determination that a substance is carcinogenic on the basis of a single unreplicated study where there are contradictory data, and it refers to saccharin, where the studies produced conflicting test results, as an example.

The Commissioner advises that the reference to saccharin is neither analogous nor applicable to the chloroform toxicity and carcinogenicity bioassays relied upon in this action. Thus far, the results of studies using saccharin have been inconclusive; additional studies are ongoing. The results of the NCI studies are conclusive. In addition, the studies submitted by CTFA were conducted at lower dosages than those reported by NCI. The lack of sensitivity of the current carcinogenesis bioassays in rodents is well recognized. Thus the positive finding with chloroform should be given greater weight than studies at lower dosages using small numbers of animals.

f. The comment noted that the proposed action had not been referred to the Toxicology Advisory Committee. The comment cited § 2.322 (21 CFR 2.322) of the proposed regulations on FDA administrative practices and procedures published in the FEDERAL REGISTER of September 3, 1975 (40 FR 40682) that states that issues involving a determination of carcinogenicity under section 409(c)(3)(A), 512(d)(1)(H), or 706(b)(5)(B) of the act will ordinarily be referred to the Toxicology Advisory Committee. The comment expressed the belief that its scientific critique of the NCI studies demonstrates compelling reasons why the matter should now be referred to the Toxicology Advisory Committee before final action is taken.

The Commissioner rejects this comment. Technically, this action does not fall under the statutory sections cited in proposed § 2.322. More importantly, the NCI report was reviewed by a panel of consultants before its release to FDA, and then by FDA scientists after it was received. Despite a number of problems, many of which are discussed in the NCI report, concurrence was reached relative to the carcinogenic effect of chloroform in animals. The action proposed by FDA was based not only in consideration of the NCI report but also on other information available, including the CTFA submissions to the FDA Bureau of Foods and the summary of updated experiments presented to the OTC Oral Cavity Products Review Panel of FDA. The necessity for referring this problem to the Toxicology Advisory Committee was discussed at an FDA Bureau of Drugs conference with CTFA representatives prior to publication of the proposal. Based on the data reviewed, discussion with the FDA Bureau of Foods, and discussions with CTFA regarding their data, the Commissioner concludes that it is not necessary to seek the advice of the Toxicology Advisory Committee.

2. One comment expresses the opinion that there is not enough documented evidence to show that products containing chloroform are indeed hazardous to health.

The Commissioner considers the fact that a substance has been shown to be an animal carcinogen must be taken as evidence that it has a potential for carcinogenesis in humans unless there is strong evidence to the contrary. No strong evidence to the contrary has been shown regarding chloroform. Further, the risk to humans through frequent and long term exposure to such a substance in human drug and cosmetic products is contrary to the public health unless the benefit of such exposure clearly outweighs the risk. Any benefits attributed to the use of chloroform in human drug and cosmetic products do not outweigh the attendant risks, particularly in view of the availability of safe and suitable alternate ingredients. The Commissioner concludes that continued use of choloroform in human drug and cosmetic products may cause such products to be injurious to health and is therefore unwarranted. The Commissioner further considers the potential risk posed by chloroform to be a problem necessitating the action taken.

3. One comment expresses the opinion that chloroform does present an imminent health hazard and urged that all drug products containing chloroform be immediately banned and removed from all stores. The comment further requests an immediate public warning urging people to avoid the use of products containing chloroform that are in their possession.

As stated in the preamble of the proposal, because there are no data to show that chloroform is a human carcinogen, and in view of the small amount of chloroform to which an individual might be exposed in using currently marketed chloroform-containing human drug and cosmetic products, the Commissioner has determined that the present risk to the public is minimal and that chloroform-containing products cannot reasonably be considered to constitute an imminent health hazard. Therefore, he does not believe it necessary for consumer protection to order a recall of all currently marketed products containing chloroform or to issue a public warning against the use of such products.

4. One comment requests an exemption from the requirements of the regulation for in vitro diagnostic products containing chloroform. The comment expresses the opinion that such exemption is necessary until legislation is passed which clearly places such products in a category other than human drugs.

The Commissioner advises that the Medical Device Amendments of 1976 (Pub. L. 94-295) became law on May 28, 1976. The new definition of "device" places all in vitro diagnostic products in the device category; therefore, this regulation is not applicable to any such products. No change in the regulation is necessary.

5. Objection was raised that the proposed action invaded a citizen's right of free choice to determine whether to use a product knowing that it may be hazardous. The comment suggests that the label should indicate the facts, good or bad, about a product, but the consumer should then be given the freedom to decide whether to use the product.

The Commissioner disagrees with this comment. Although chloroform-containing human drug and cosmetic products have been on the market for many decades and may have been generally recognized as safe, recent evidence showing chloroform to be an animal carcinogen and its potential for carcinogenesis in humans no longer permit this conclusion. Where scientific evidence indicates that a particular product is no longer safe, the Federal Food, Drug, and Cosmetic Act prohibits its further marketing unless its safety can be demonstrated.

6. Several comments request that the final regulation both permit the continued use of chloroform in the manufacturing process of a human drug or cosmetic product and allow for unavoidable trace residues in the finished product. Some of the comments state that chloroform may occur as an unintended byproduct of the chemical reaction by which the active ingredient in a prescription drug product is synthesized and that total removal of such trace quantities would be technically unfeasible, if not impossible.

The Commissioner advises that the regulation is applicable only to human drug and cosmetic products containing chloroform as an active or inactive ingredient. He further advises that the regulation is not applicable to situations where chloroform is present in residual amounts due to its use as a processing solvent during manufacture of a drug or cosmetic product or to the presence of residual amounts of chloroform as a byproduct resulting from the synthesis of an ingredient in a drug or cosmetic product. The regulation has been revised to clarify this point. The problem raised by the comments is an industrywide problem that is of concern to several government agencies. The FDA is studying the problem intensively to determine the level and extent of chloroform in finished drug and cosmetic products as a result of the manufacturing process and is seeking a resolution of the issue. The Commissioner's decision will be the subject of a separate FEDERAL REGISTER notice if additional steps are necessary to protect the public health.

7. Comments request a change in the proposed effective date of July 8, 1976, to allow firms to dispose of inventories of products which were manufactured or in the process of being manufactured at the time of publication of the proposal on April 9, 1976. One comment states that, if July 8 is the cutoff date for distribution as proposed, manufacturers will be forced to discard existing stocks of these products and will be deluged with stocks returned from the wholesale and retail trade levels. Further, such action could result (1) in the Commissioner's Inflation Impact Analysis being invalid since these costs, which would ultimately be passed to consumers, were

not given adequate consideration and (2) shortage of cough-cold preparations could develop during the coming cold season.

The Commissioner has given extensive consideration to this issue and realizes that the regulation, when effective, will result in destruction of stocks of human drug and cosmetic products on hand at the manufacturer, repacker, relabeler, or own-label distributor levels or those that may be returned from a wholesaler or retailer. He points out, however, that, in the proposal, industry was encouraged to replace chloroform-containing products with reformulated products as soon as possible and in advance of the publication of the final regulation. The potential risk posed by chloroform does not justify continued shipment or use of chloroform-containing human drug and cosmetic products. Therefore, after the effective date of these regulations, any human drug product containing chloroform that is introduced or delivered for introduction into interstate commerce is a new drug and misbranded, and is subject to regulatory action under sections 301, 502, and 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 352, and 355). Likewise, after this effective date, any cosmetic product containing chloroform as an ingredient that is introduced or delivered for introduction into interstate commerce is adulterated under section 601(a) of the act (21 U.S.C. 361(a)) and subject to regulatory action. The effective date of these regulations has been extended to July 29, 1976 in that time needed for review of the comments exceeded that originally anticipated. The Commissioner believes that this date should be adhered to in view of all the considerations extensively discussed in the preamble to the proposal. He also believes that this will allow for an orderly replacement of chloroform-containing drug and cosmetic products at the retail level and that there will be an ample supply of such products on the market until reformulated products reach the distribution channels.

The Commissioner advises that in the FEDERAL REGISTER of June 10, 1976 (41 FR 23449), the availability of the NCI report and additional background information was announced by the National Institutes of Health.

The Commissioner also advises that copies of the following references are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852:

1. Bio/dynamics Inc., "A Subacute Toxicity Study of Chloroform in Mice," April 9, 1976.

2. Hill et al., "Genetic Control of Chloroform Toxicity in Mice," *Science*, 190:159, 1975.

3. Charlesworth, F. A., "Patterns of Chloroform Metabolism," *BIBRA Information Bulletin*, 14:225, 1975.

4. Grasso, P. and R. F. Crampton, "The Value of the Mouse in Carcinogenicity Testing," *BIBRA Information Bulletin*, 1975.

5. Cueto, C., Jr. and W. D'Aguanno, memorandum of telephone conversation June 3, 1976.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 301, 502, 505, 601(a), 701(a), 52 Stat. 1042-1043, 1050-1055, as amended (21 U.S.C. 331, 352, 355, 361(a), 371(a))) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. In Part 310, new § 310.513 is added to read as follows:

§ 310.513 Chloroform, use as an ingredient (active or inactive) in drug products.

(a) Chloroform has been used as an ingredient in drug products, such as cough preparations, liniments, and toothpastes. Although considered safe for many years, recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats.

(b) Any drug product containing chloroform as an ingredient is a new drug within the meaning of section 201 (p) of the act and misbranded and is subject to regulatory action under sections 301, 502, and 505 of the act. Any drug product containing chloroform in residual amounts from its use as a processing solvent during manufacture, or as a byproduct from the synthesis of an ingredient, is not, for the purpose of this section, considered to contain chloroform as an ingredient.

(c) Any holder of an approved new drug application for a drug product containing chloroform as an ingredient shall submit to the Food and Drug Administration on or before July 29, 1976 a supplemental application providing for a revised formulation removing chloroform as an ingredient.

(1) The supplemental application shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) The date that the composition of the drug product will be changed.

(iii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iv) Data available to establish the stability of the revised formulation and, if the data are too limited to support a conclusion that the drug will retain its declared potency for a reasonable marketing period, a commitment from the applicant:

(a) To test the stability of marketed batches at reasonable intervals;

(b) To submit the data as they become available; and

(c) To recall from the market any batch found to fall outside the approved specifications for the drug.

(v) Copies of the label and all other labeling to be used for the drug product (a total of 12 copies if in final printed form, 4 copies if in draft form).

(2) If such drug product now contains more than one percent chloroform, the revised formulation containing no chloroform shall not be marketed before the receipt of written notice of approval of the supplemental application by the Food and Drug Administration.

(3) If such drug product now contains one percent or less chloroform, the revised formulation containing no chloroform may be marketed, subject to the conditions of § 314.8(e) of this chapter, after submission of the supplemental application but prior to the receipt of written notice of its approval by the Food and Drug Administration.

(d) Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND notice) for a drug product containing chloroform as an ingredient shall amend the IND notice on or before July 29, 1976 to revise the formulation removing chloroform as an ingredient.

(e) The Commissioner will initiate action to withdraw approval of an application or terminate an IND notice in accordance with the applicable provisions of section 505 of the act and Parts 312 and 314 of this chapter upon failure of a holder of an approved new drug application or sponsor of an IND notice to comply with the provisions of paragraph (c) or (d) of this section.

2. In Part 700, new § 700.18 is added to read as follows:

§ 700.18 Use of chloroform as an ingredient in cosmetic products.

(a) Chloroform has been used as an ingredient in cosmetic products. Recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats. Scientific literature indicates that chloroform is absorbed from the gastrointestinal tract, through the respiratory system, and through the skin. The Commissioner concludes that, on the basis of these findings, chloroform is a deleterious substance which may render injurious to users any cosmetic product that contains chloroform as an ingredient.

(b) Any cosmetic product containing chloroform as an ingredient is adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act. Any cosmetic product containing chloroform in residual amounts from its use as a processing solvent during manufacture, or as a byproduct from the synthesis of

an ingredient, is not, for the purpose of this section, considered to contain chloroform as an ingredient.

Effective date: These regulations shall become effective July 29, 1976.

(Secs. 301, 502, 505, 601(a), 701(a), 52 Stat. 1042–1043, 1050–1055, as amended (21 U.S.C. 331, 352, 355, 361(a), 371(a)).)

Dated: June 24, 1976.

SAM D. FINE,
Associate Commissioner for Compliance.

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